Aging is a complex, multifactorial process resulting in several functional and esthetic changes in the skin. These changes result from intrinsic as well as extrinsic processes, such as ultraviolet radiation. Recent advances in skin biology have increased our understanding of skin homeostasis and the aging process, as well as the mechanisms by which ultraviolet radiation contributes to photoaging and cutaneous disease. These advances in skin biology have led to the development of a diversity of treatments aimed at preventing aging and rejuvenating the skin. The focus of this review is the mechanism of photoaging and the pathophysiology underlying the treatments specifically designed for its prevention and treatment. (J Am Acad Dermatol 2006;55:1-19.)

**Learning objectives:** At the conclusion of this learning activity, participants should be familiar with the mechanism of photoaging, the treatments for photoaging, and the data that supports the use of these treatments.

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**Abbreviations used:**
- AHA: α-hydroxy acid
- AP: activator protein
- CoQ10: coenzyme Q10
- CO2: carbon dioxide
- GA: glycolic acid
- GTP: green tea polyphenols
- HA: hyaluronic acid
- IL: interleukin
- MMP: matrix metalloproteinase
- NF: nuclear factor
- RA: retinoic acid
- RAR: retinoic acid receptor
- ROS: reactive oxygen species
- RXR: retinoid x receptor
- SNAP: synaptosomal associated membrane protein
- SPF: sun protection factor
- TGF: transforming growth factor
- TIMP: tissue inhibitors of matrix metalloproteinases
- TNF: tumor necrosis factor
- UPF: ultraviolet protection factor
- UV: ultraviolet radiation
- YAG: yttrium-aluminum-garnet

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The aging process encompasses progressive physiological changes in an organism that lead to senescence; it refers to the decline of biological functions and the organism’s ability to adapt to metabolic stress with time.1 Many cultures revere the elderly as a source of wisdom. However, in western societies there is a stigma associated with aging.2 The search for rejuvenation is as old as humankind and is reflected in ancient stories, including the Greek Argonauts and the Fountain of Youth, where the extensive efforts taken to restore youth are illustrated.3

More and more, individuals are seeking treatment for reversal of age-associated changes in skin. Patients are benefiting from recent advances by the medical and cosmeceutical industries that increase our understanding of skin homeostasis and the aging process. Our perception of age as well as beauty is largely dependent on the appearance of exposed skin,4 and its condition is dictated in part by environmental effects, especially ultraviolet (UV) light.5 This article reviews the mechanisms of UV-induced skin aging and discusses the compounds that have been shown, or have potential, to improve the appearance of photoaged skin.

**THE AGING PROCESS**

The basic biologic processes involved in aging lead to reductions in function and ability to tolerate
injury. There are two general theories of aging. The first states that aging is a preordained process that is genetically determined. Support for this theory comes from telomere lengths, the terminal portions of chromosomes that shorten at every cell cycle. Once the telomeres reach a critical length, cell cycle arrest or apoptosis occurs. Furthermore, primary cell cultures cannot continue to replicate indefinitely, thought by some to be a cancer-prevention strategy.

Another theory suggests that aging is largely due to cumulative environmental damage. For example, free radicals can be generated from oxygen during normal metabolism and likely contribute to this process. Organisms have evolved cellular defense systems against the toxicity of free radicals, particularly oxygen-based free radicals, or reactive oxygen species (ROS). Longer lived species have higher degrees of enzymatic protection against ROS. The activity of antioxidant enzymes and the levels of nonenzymatic antioxidants decline with age, allowing oxidative damage to occur.

In the skin, both genetic and environmental mechanisms likely contribute to the aging process. For instance, environmental factors such as UV radiation can damage telomeres and induce ROS, thereby inducing cellular senescence. Thus genetic processes and environmental effects may share a common final pathway.

STRUCTURE, FUNCTION, AND AGE-RELATED CHANGES IN THE SKIN

A major function of the skin is to protect the organism from physical and environmental assaults. These stressors come in many forms; solar radiation, infection, temperature extremes, dehydration, and mechanical trauma are but a few. The skin also possesses and mediates immune, endocrine, and neural functions. All of these functions can decline with age (Table I).

PHOTOAGING OF SKIN

Beyond the intrinsic aging process, sun-exposed areas such as the face, neck, and dorsum of hands and forearms encounter additional damaging effects, largely due to exposure to UV. Photaging refers to the effects of long-term UV exposure and sun damage superimposed on intrinsically aged skin. It affects lighter skinned individuals most severely. Many of the functions of skin that decline with age show an accelerated decline in photoaged skin.

Clinical alterations

The clinical signs associated with photoaging are dyspigmentation, laxity, a yellow hue, wrinkles, telangiectasia, a leathery appearance, and cutaneous malignancies. Old, photoprotected skin may have increased laxity and fold accentuation, but it is thin and lacks signs of actinic damage. Seborrheic keratoses are common benign proliferative growths characteristic of aged skin and may be related to sun exposure. Specific phenotypes resulting from sun exposure, such as actinic elastosis and Favre–Racouchot syndrome (nodular elastosis with cysts and comedones), are also well described.

Histopathologic alterations

Histopathologically, photoaged skin may show a loss of epidermal polarity or orderly maturation of keratinocytes. Individual keratinocytes are characterized by atypia, especially in the lower epidermal layers. The thickness of sun-protected epidermis may decrease with age, although it has been reported that it remains fairly constant. However, epidermal thickness is greater in sun-exposed skin. There is a flattening of the dermoepidermal junction that can lead to the appearance of atrophy, such as that seen in poikiloderma.

Overall, the cell population of the photoaged dermis increases; fibroblasts are numerous and hyperplastic, and inflammatory infiltrates abound. This chronic inflammation in photoaged skin is termed heliodermatitis. The microvasculature is also altered and vessel walls are thickened with deposition of a basement membrane–like material. Fibroblasts in photoaged skin are elongated and collapsed. Decreases in type I and III collagen are seen in intrinsically aged skin; however, these decreases are accelerated in sun-exposed regions. Interestingly, fibroblasts from photodamaged skin are able to produce collagen in culture similar to cells from sun-protected aged skin. Thus an intrinsic difference in synthesis is not thought to be responsible for decreases in collagen seen with photodamaged skin.

Elastin quantity decreases with age, yet in sun-exposed skin the quantity of elastin increases in proportion to the amount of sun exposure. Elastin has been shown to be induced in vitro by UV radiation. The accumulated elastin in the skin appears abnormal and seems to occupy the areas previously held by collagen. It has been suggested that the increase in abnormal elastin results from a biphasic process beginning with hyperplasia of normal elastic tissue. The elastin becomes abnormal in appearance because of the effects of chronic inflammation.

Photodamage is manifested primarily as the disorganization of collagen fibrils that constitute the bulk of the connective tissue and the accumulation of abnormal, amorphous, elastin-containing material.
Solar elastosis is used to describe the accumulation of elastin material associated with prolonged sun exposure (Fig 1).27 Fine wrinkles are a prominent feature of both intrinsically aged and photoaged skin; a precise histological correlate has not been identified.52

**UV RADIATION AND SKIN BIOLOGY**

UV radiation has numerous direct and indirect effects on the skin. It is estimated that approximately 50% of UV-induced damage is from the formation of free radicals, whereas direct cellular injury and other mechanisms account for the remainder of UV effects.53

**Molecular and genetic changes**

The molecular changes in DNA induced by UV radiation have been studied extensively in relation to photocarcinogenesis. Chromophores in tissue absorb energy and reach “excited states.” They then either undergo chemical changes, transfer their energy to other molecules, or give off the extra energy as light or heat.54

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**Table I.** Skin components and systems: functions and changes with age

<table>
<thead>
<tr>
<th>Cell type/component/system</th>
<th>Function</th>
<th>Change with age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratinocytes</td>
<td>Numerous eg, barrier function, mechanical protection, cytokine production, cell signaling14</td>
<td>↓ Proliferation and differentiation6</td>
</tr>
<tr>
<td>Melanocytes</td>
<td>Synthesize pigment for protection from UV radiation18,19</td>
<td>↓ Cell signaling and growth factor response15,16</td>
</tr>
<tr>
<td>Langerhans cells</td>
<td>Antigen presentation14</td>
<td>↓ Barrier function with injury17</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>Synthesis and degradation of ECM</td>
<td>↓ Melanocyte number6</td>
</tr>
<tr>
<td>Collagen</td>
<td>ECM component</td>
<td>↓ Life span and growth factor response20</td>
</tr>
<tr>
<td>Elastin</td>
<td>ECM component</td>
<td>↓ In number6</td>
</tr>
<tr>
<td>Tissue inhibitors of matrix metalloproteinases</td>
<td>Protect collagen and elastin from endogenous breakdown systems</td>
<td>↓ Growth factor response23</td>
</tr>
<tr>
<td>Dermal vascular bed</td>
<td>Thermoregulation</td>
<td>↓ Biosynthesis24</td>
</tr>
<tr>
<td>Subcutaneous fat</td>
<td>Thermoregulation, energy storage</td>
<td>↑ Stability and resistance to enzymatic degradation25</td>
</tr>
<tr>
<td>Endocrine system—vitamin D</td>
<td>UV protection,40 calcium homeostasis</td>
<td>↓ Microfibril content26</td>
</tr>
<tr>
<td>Endocrine system—estrogen</td>
<td>Improves collagen content and quality, increase skin thickness, enhance vascularization12</td>
<td>↓ Porous, indistinct, and fragmented appearance27</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Sensation, thermoregulation</td>
<td>↓ Function28</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td>↓ Facial innervation, ↑ truncal innervation35</td>
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<tr>
<td></td>
<td></td>
<td>↓ Tolerance to cold exposure36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed wound healing37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Ability to repair DNA damage38</td>
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<tr>
<td></td>
<td></td>
<td>↓ Function of early population doubling level of cDNA-1, an inhibitor of angiogenesis39</td>
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</table>

ECM, extracellular matrix; UV, ultraviolet.

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UV radiation from 245 to 290 nm is absorbed maximally by DNA,55 thus implicating UVB as a primary mutagen.56 UVB-induced DNA mutations occur by chemical change and include cyclobutane pyrimidine dimers and (6-4) photoproducts formed between adjacent pyrimidine bases (Fig 2).57 Other DNA photoproducts have been reported, such as cyclobutane pyrimidine dimers and (6-4) photoproducts.
as cytosine photohydrates, that are produced at low efficiency in experimental systems. These DNA mutations may be clinically related to specific signs of photoaging as wrinkling, increases in elastin, and collagen damage are observed in animals exposed to UVB. However, specific mechanisms by which DNA photoproducts lead to the photodamaged phenotype have not been elucidated.

UVA, and to a lesser extent UVB, can damage DNA indirectly through the generation of ROS (Fig 2). These include superoxide anion, peroxide, and singlet oxygen. ROS damage cellular DNA as well as lipids and proteins. Mutagenesis by UVA may involve trans-urocanic acid and results in the production of singlet oxygen and DNA nicks. 8-Hydroxy guanine is also a product of UVA mutagenesis via ROS induction.

A recently recognized 4977 base-pair deletion of mitochondrial DNA (the “common deletion”) is found in fibroblasts in the dermal compartment of photoaged skin. It is induced by UVA via ROS in vitro and in vivo and is considered a marker for UVA damage. The mitochondrion, responsible for aerobic energy production, has the highest ROS turnover in the cell. Many of the genes involved in this process are encoded in the mitochondrial DNA, and mutations in the mitochondrial genome may be associated with the functional changes seen with aging.

Effects on pigmentation
Sun exposure contributes to pigmenary changes. Suntan occurs in two steps: immediate pigment darkening, occurring in individuals with Fitzpatrick skin types III-IV, and delayed formation of new melanin. Immediate pigment darkening reaches its maximal state seconds after UV exposure and results from redistribution of melanin. Delayed tanning is associated with an increase in the activity and

**Fig 2.** Effects of UV light on the keratinocyte (KC) and fibroblast (FB). UV induces reactive oxygen species (ROS) which can damage DNA (△) or can inhibit tyrosine phosphatases, leading to increased signal transduction and ultimately up-regulation of AP-1 transcription factor. UV can also directly up-regulate c-Jun, a component of AP-1, and can down-regulate retinoic acid (RA) receptors, which decreases RA inhibition of AP-1. Further effects of UV include direct DNA mutagenesis (△), up-regulation of nuclear factor-κB (NF-κB), and down-regulation of TGF-β signaling. These effects have been related to collagen production and breakdown, as well as to inflammatory cytokine production. AP-1, Activator protein 1; ECM, extracellular matrix; MMP, matrix metalloproteinase; ROS, reactive oxygen species.
number of melanocytes. Its function is photoprotection.

Lentigines and guttate hypomelanosis are typically found on sun-exposed skin and are considered a consequence of UV exposure. However, the mechanisms of their induction by UV radiation are not clear. Histologically, lentigines show a considerable increase in melanosome content of the basal keratinocytes. Melanocytes have an increased capacity for melanin production, and in some samples the number of melanocytes is increased. In guttate hypomelanosis, decreases in melanin content as well as melanocyte number are seen. Remaining melanocytes display abnormal morphology.

Inflammation and vasodilation result from UV exposure, and this is clinically manifested as a sunburn. The transcription factor nuclear factor (NF)-κB is activated by UV radiation; this is thought to be the initial step in the inflammation of sunburn reactions (Fig 2). NF-κB activation leads to increases in the proinflammatory cytokines interleukin 1 (IL-1), IL-6, vascular endothelial growth factor, and tumor necrosis factor (TNF)-α, attracting neutrophils that contain preformed neutrophil collagenase (MMP-8) (Fig 2). NF-κB is also activated by UV light via an iron-dependent mechanism. Iron is required for the activation of MMP-1, the major metalloproteinase responsible for collagen degradation (Fig 2). ROS oxidize and thereby inhibit protein-tyrosine phosphatases which function to down-regulate these receptors, thereby resulting in receptor up-regulation (Fig 2).

This increased receptor activation is thought to lead to activation of signaling kinases throughout the skin, although the precise mechanism is unknown. The nuclear transcription factor activator protein 1 (AP-1) is ultimately expressed and activated. AP-1 controls transcription of matrix metalloproteinases (MMPs), enzymes responsible for degradation of the extracellular matrix. The MMPs include metalloproteinase-1 (a collagenase), MMP-3 (stromelysin), and MMP-9 (92-kd gelatinase). MMP expression is localized in both epidermal keratinocytes as well as in dermal fibroblasts. Iron is required for the activation of MMP-1, the major metalloproteinase responsible for collagen degradation (Fig 2). ROS therefore directly contribute to tissue oxidation and degradation as well as interfere with signal transduction pathways involved in the expression of genes that are important regulators of collagen metabolism.

Like AP-1, the transcription factor NF-κB is also activated by UV light via an iron-dependent mechanism. It amplifies the UV response by stimulating the transcription of inflammatory cytokines and attracting neutrophils that contain preformed neutrophil collagenase (MMP-8) (Fig 2). NF-κB is also able to increase expression of MMP-9.

MMP up-regulation can occur after only a minimal dose of UV, well below that required to produce erythema. Furthermore, there is a dose-response relationship between UV exposure and MMP induction. Exposure to UV light that is insufficient to cause sunburn can therefore facilitate the degradation of skin collagen and, presumably, eventual photoaging. Minimal repetitive exposures to UV light at a dose equivalent to 5 to 15 minutes of exposure to midday sun on an every-other-day basis is sufficient to maintain these elevated levels of MMP.

Collagen production is reduced in photoaged skin. After UV irradiation, the procollagen pool may have arisen to prevent an autoimmune response to inflammatory products resulting from UV-mediated damage (eg, UV-damaged DNA).

UV effects on the extracellular matrix

Accumulating evidence from in vitro studies suggests that UV radiation mimics the actions of receptor ligands via the generation of ROS. Within 15 minutes after UV exposure, receptors for epidermal growth factor, IL-1, and TNF-α are activated in keratinocytes and fibroblasts. It is postulated that ROS oxidize and thereby inhibit protein-tyrosine phosphatases which function to down-regulate these receptors, thereby resulting in receptor up-regulation (Fig 2).

Immunosuppression

UV irradiation has also been implicated in local and systemic immunosuppression, which may have implications in cutaneous tumor surveillance. Langerhans cells undergo numeric, functional, and morphologic changes after UV exposure, resulting in their depletion from the skin. Decreases in contact hypersensitivity responses as well as delayed-type hypersensitivity occurring after UV exposure have been noted. This immunosuppression is partially mediated by DNA damage as well as by altered cytokine expression. Increased production of the immunosuppressive cytokine IL-10 has been noted in the cutaneous inflammatory infiltrates after exposure to UV. UV-induced immunosuppression
is markedly decreased and notably absent by 24 hours after exposure in vivo. AP-1 and transforming growth factor (TGF)-β are involved in this UV-mediated down-regulation of collagen synthesis (Fig 2). AP-1 is composed of two subunits, the constitutively expressed c-Fos and the UV-inducible c-Jun. Overexpression of the c-Jun component of AP-1 in cultured fibroblasts can decrease expression of type I collagen (Fig 2). In addition, decreased expression of TGF-β2 and its receptor is noted throughout the epidermis and dermis after UV irradiation. TGF-β is an important promoter of collagen synthesis, and its predominant subtype in human skin is thought to be TGF-β2.

Finally, damaged collagen itself may also down-regulate new collagen synthesis. When dermal fibroblasts are incubated in contact with type I collagen that has been degraded by MMP in vitro, synthesis of type I procollagen is decreased. Similar effects are seen in vivo. Mechanical effects are thought to contribute to this decreased collagen synthesis in the photoaged dermis. Collagen production occurs most efficiently in cells that maintain a high mechanical tension. Impaired spreading and attachment of fibroblasts onto degraded collagen may contribute to inhibition of collagen synthesis. A cycle is formed by which decreased production of new collagen due to poor adhesion of fibroblasts to damaged collagen leads to progressively worse photodamage.

The sequence of events observed in photoaging can be compared with that in wound healing. Tissue inhibitors of metalloproteinases are part of this response, but like all wound healing, the process is not perfect. The result is a minute defect referred to as a solar scar. The accumulation of these over many years via multiple exposures to UV light is thought to contribute to the photoaged phenotype.

Retinoic acids and photodamage

The retinoic acid (RA) family constitutes several compounds including vitamin A (all-trans-retinol) and its natural and synthetic derivatives, known as retinoids. RA is important for normal epithelial growth and differentiation as well as for maintenance of normal skin homeostasis. RA compounds have been shown to negatively regulate AP-1.

RA compounds exert their effects through two families of nuclear receptors, namely, retinoid acid receptors (RARs) and retinoid X receptors (RXRs). UV radiation rapidly decreases the expression of the two predominant retinoid receptors in human skin, RAR-γ and RXR-α, in vivo. This is associated with a near complete loss of the induction of RA-responsive genes. In UVB-irradiated cultured keratinocytes and melanocytes, these receptors are also decreased. This is normalized in melanocytes within 2 to 3 days, but not in keratinocytes. A decrease in the receptors for the RAs may allow an increase in activity of the AP-1 pathway, further increasing MMP activity (Fig 2). As such, UV irradiation results in a functional deficiency of vitamin A in the skin.

INHERENT DEFENSE MECHANISMS AGAINST UV RADIATION

Numerous endogenous mechanisms protect the skin from UV-induced damage. These include increased epidermal thickness, pigment, DNA repair mechanisms, apoptosis, tissue inhibitors of metalloproteinase, and antioxidants. Apoptotic mechanisms and endogenous antioxidants are thought to decline with age. Thus, over a lifetime, these protective mechanisms may be overwhelmed, allowing the skin to succumb to the hazards of UV exposure, leading to photoaging and other conditions, such as skin cancer.

Epidermal thickness

An increase in epidermal thickness occurs after UV exposure and helps protect from further UV damage. Increased epidermal and dermal mitotic activity has been reported about 24 to 48 hours after acute UV exposure. The importance of stratum corneum thickening in photoprotection has been demonstrated in patients with vitiligo who lack melanin in specific areas.

Pigment

The protective role of melanin pigment should not be underestimated. Black skin differs from white skin with respect to the size and number of melanosomes as well as aggregation pattern within melanocytes and keratinocytes. Compared with black skin, white skin shows more dermal DNA photodamage, infiltrating neutrophils, keratinocyte activation, and IL-10 expression after UV exposure. Levels of MMPs are also increased. Thus the distribution of melanin is thought to provide protection from sunburn, photoaging, and carcinogenesis by absorbing and scattering detrimental UV rays.

Repair of DNA mutations and apoptosis

With UV-induced DNA damage, p53 transcription is activated and the cell is arrested in G1 phase to allow for DNA repair. UV-induced mutations such as cyclobutane pyrimidine dimers and (6-4) photoproducts are repaired by endogenous mechanisms such as the nucleotide excision repair system. If the damage is too severe, apoptosis may occur. “Sunburn cells” describe keratinocytes undergoing apoptosis and therefore serve as a histologic marker.
of UV damage. They can be found as early as 30 minutes after exposure to UV irradiation. An age-associated decrease in sunburn cell induction by UV irradiation is noted, which suggests that apoptotic mechanisms decline with age. If DNA repair mechanisms or apoptosis should fail, cutaneous tumorigenesis may result.

Tissue inhibitors of MMPs
Tissue inhibitors of MMPs (TIMPs) regulate the actions of MMP. Conflicting results have been found regarding the responses of TIMPs to UV irradiation. In a fibroblast culture, both TIMP-1 and TIMP-2 levels were decreased in a dose-dependent fashion after UV exposure. However, UV has been shown to induce TIMP-1 in vivo.

Antioxidants
The skin is equipped with enzymatic as well as nonenzymatic cutaneous antioxidants. Endogenous antioxidants include vitamin E, coenzyme Q10 (CoQ10), ascorbate, and carotenoids, whereas enzymatic antioxidants include superoxide dismutase, catalase, and glutathione peroxidase. These provide protection from ROS produced during normal cellular metabolism. Excessive exposure to UV radiation is thought to overwhelm and deplete this antioxidant supply, thereby leading to a state of oxidative stress. Concentrations of carotenoids are lower in human cutaneous malignancies, such as basal cell carcinoma, suggesting that these antioxidants are important in the skin’s defense against UV radiation and photocarcinogenesis.

UV radiation can influence endogenous antioxidant enzyme levels. After a single low or moderate dose of UV radiation, there is an initial decrease in antioxidant enzyme transcript levels in cultured fibroblasts. This is followed by an up-regulation of superoxide dismutase and glutathione peroxidase above baseline levels by day 5. In a separate experiment examining irradiated fibroblasts, catalase and superoxide dismutase both decreased and recovered only to baseline levels at 5 days after a single exposure to UV radiation. Both studies clearly demonstrated an initial decrease in antioxidant enzyme activity, which lasted for days. Repeated UV exposures before enzyme activity returns have the potential to lead to increased tissue damage.

TREATMENT OF PHOTOAGING
Strategies for medical treatment and intervention for photoaging can be categorized into a unique paradigm based on disease prevention. Primary prevention refers to the reduction of risk factors before a disease or condition has occurred. The goal of secondary prevention is early detection of disease, potentially while still asymptomatic, to allow positive interference to prevent, postpone, or attenuate the symptomatic clinical condition. Tertiary prevention is the treatment of an existing symptomatic disease process to ameliorate its effects or delay its progress.

Primary prevention
Sun protection. Perhaps the single most cost effective therapy that can be offered to patients is sun protection in the form of sun avoidance, sun-protective clothing, and sunscreens. Peak times for UV exposure are between 10 am and 4 pm, and sun avoidance should be encouraged during this time. Clothing, hats, and sunglasses that protect from sun exposure should be part of a package of protection. Photoprotective clothing is rated using the UV protection factor (UPF), which utilizes a defined source of UV and a photodetector to measure the amount of radiation transmitted through a sample of fabric. The UPF is calculated as a ratio of these two measurements with an allowance for the differing biologic effectiveness of the various wavelengths in UV radiation. A UPF of 40 to 50 provides excellent UV protection transmitting less than 2.6%
of effective UV radiation. Regular summer clothing typically has a UPF of 10 or higher and therefore provides protection equivalent to that of an SPF 30 sunscreen in normal use.

Sunscreens have traditionally been divided into chemical agents, which absorb specific photons of UV light, and physical agents (sunblock), which reflect or scatter radiation. UVB-absorbing sunscreens include p-aminobenzoic acid and its esters (padimate A and O), the cinnamates, and salicylates. UVA sunblocks contain titanium dioxide or zinc oxide, whereas UVA-absorbing sunscreens include avobenzone (Parsol 1789) and terephthalylidene dicamphor sulfonic acid. Parsol 1789 can degrade quickly unless it is stabilized. Zinc oxide has been shown to provide better protection against UVA than titanium dioxide.

The sun protection factor (SPF) is an internationally accepted standard by which the efficacy of sunscreens is assessed. The determination of the SPF is based on the minimal erythema dose of solar-simulated radiation and hence the prevention of mainly UVB-mediated erythema. Since UVA also has a role in photoaging, SPF may be a poor guide to the ability of a sunscreen to protect against photoaging. Sunscreens containing both UVA and UVB protection may permit as much as 50% of UVA-induced free radical production even if they have a high SPF and are applied at the recommended dose (2 mg/cm²). Sunscreens with greater UVA blocking or absorbing ability may better protect against photodamage. Some sunscreens are not effective in their protection from UV-induced photodamage even when properly applied and should therefore be regarded as an important but adjuvant therapy.

In animal studies, sunscreens have been shown to prevent photodamage and allow for its repair. Although direct clinical evidence is lacking, indirect evidence that sunscreens allow for repair of photodamage comes from numerous clinical trials in which sunscreens are used in both control and treatment arms. For example, in one study use of sunscreen with an SPF of at least 15 produced an improvement in photodamage compared with baseline after 24 weeks.

### Secondary prevention

**Retinoids.** For years, retinoids have been the mainstay of topical therapy for the prevention and treatment of photoaging. Retinoid (all-trans-retinoic acid), a nonselective agent that activates all RARs directly and RXRs indirectly, has been shown to improve the clinical signs of photoaging in controlled clinical trials. Several weeks of

<table>
<thead>
<tr>
<th>Table II. Evidence for antiaging therapies</th>
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<tr>
<td><strong>Type of intervention</strong></td>
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<td>--------------------------</td>
</tr>
<tr>
<td>Retinoids</td>
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<td>Hormonal</td>
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<td>Growth factors and cytokines</td>
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<td>New compounds</td>
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<td>Botulinum toxins</td>
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<td>Soft tissue augmentation</td>
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Evidence categories: A1, Randomized, controlled, double-blind trial, N > 100; A2, randomized, controlled, double-blind trial, N < 100; B, randomized, controlled, single-blind trial or controlled, double-blind, nonrandomized trial; C, controlled trial (treatment vs placebo); D1, observational study, >1 treatment group, double blind; D2, observational study, no blinding.

treatment are required before clinical improvement is appreciated. The greatest obstacle to tretinoin use is irritation in the form of erythema, peeling, and stinging, which decline with continued use.

The benefits of retinoids are thought to be mediated at least in part by their effects on collagenase induction. Pretreatment with all-trans-retinoic acid inhibits UV-mediated induction of c-Jun protein, AP-1, and MMP. Pretreatment also reduces loss and inhibits UV-mediated induction of c-Jun protein, AP-1, and MMP.100 Partial restoration of markedly reduced collagen appears to be responsible for the observed clinical improvement.

Tazarotene is a second-generation retinoid that selectively binds RAR- and RAR-β. Like tretinoin, tazarotene is effective in the treatment of photodamage. Reduced atypia and restoration of keratinocyte polarity have also been noted after tazarotene therapy. In a 24-week randomized, controlled, double-blind study, treatment with 0.1% tazarotene resulted in significant improvement in numerous clinical assessments of photodamage. Additional clinical improvement occurred during an open-label extension and had not reached a plateau by week 52. When compared with a standard dose of tretinoin, a high-dose tazarotene regimen produced faster improvements in fine wrinkling and mottled pigmentation. Tazarotene is also a strong irritant and, like tretinoin, is thought to inhibit AP-1–dependent gene expression.

An active area of research is the development of receptor-selective retinoids to optimize therapy and minimize side effects. Up-regulation of RA-response elements and the antagonizing actions of AP-1 are not linked, which suggests that receptor-selective retinoids hold promise.

**Antioxidants.** Numerous antioxidants have been analyzed for their ability to prevent or reverse clinical signs associated with photoaging secondary to ROS. Strategies utilizing endogenous skin antioxidants as well as plant-derived or chemical compounds have been examined.

**Topical vitamin C.** Vitamin C, a potent antioxidant, has been shown to prevent erythema and sunburn cell formation after UV exposure. Vitamin C can also up-regulate collagen and TIMP synthesis in human skin. Because of the short half-life of vitamin C, skin care formulations commonly include its derivatives, which do not penetrate the skin as readily. However, in a 6-month, double-blind, placebo-controlled, randomized trial examining the use of a topical vitamin C compound, a significant decrease in wrinkles was found when measured by optical profilometry. Profilometry is a technique that utilizes skin replicas measured with special image processing software (optical profilometry) or laser (laser profilometry) to obtain an objective quantification of the skin surface topography.

**Oral supplements.** Oral supplements offer a systemic method to treat photoaging. An oral supplement containing a combination of l-proline, l-lysine, manganese, copper, zinc, quercetin, grape seed extract, N-acetyl d-glucosamine, and glucosamine sulfate was shown to improve wrinkles by 34% in a pilot study when measured by optical profilometry. Another oral supplement composed of a combination of vitamin E, vitamin C, carotenoid, selenium, and proanthocyanidin led to a significant decrease in induction of MMP after UV exposure. A reduction in UV-induced erythema was also noted, but it did not reach statistical significance.

**CoQ10.** CoQ10 is a component of the mitochondrial electron transport chain; it also acts as an antioxidant in the skin, with 10-fold higher levels in the epidermis than the dermis. Topical CoQ10 use led to significant reductions in wrinkle measurements assessed by optical profilometry in a vehicle-controlled 6-month pilot study.

**α-Lipoic acid.** α-Lipoic acid is an antioxidant and anti-inflammatory agent that has been previously shown to reduce the production of transcription factors such as NF-κB and indirectly affect the gene expression of inflammatory cytokines. Treatment with α-lipoic acid has led to significant improvements in clinical and objective measurements of photodamage, including laser profilometry.

**Estrogens.** In a cross-sectional analysis, oral estrogen use was associated with a statistically significant decrease in the risk for dry skin and wrinkling, but not atrophy. These clinical changes may be due to an increase in collagen content. Topical estrogen therapy can also lead to significant increases in collagen, firmness, and elasticity, as well as wrinkle depth measured by optical profilometry.

**Growth factors and cytokines.** Topical application of a combination of growth factors and cytokines has been evaluated in a pilot study for its effect on photoaged skin. A majority of patients showed clinical improvement in at least one facial area and a significant change in objective measurements by optical profilometry. In addition, new collagen formation was observed in biopsy specimens.

**New compounds.** The fucose-rich polysaccharide “FROP-3” increases glycosaminoglycan biosynthesis in fibroblast cultures. In a pilot study examining skin-surface microrelief, the pattern of fine wrinkling found in skin of any age, a cream containing FROP-3 showed a 10- to 15-year decrease in apparent age after 4 weeks of treatment in a
majority of patients. Skin-surface microrelief changes predictably with age, with younger persons having a regular pattern of fine, thin lines. Wrinkles become deeper and thicker with increasing age.

In a 5-week pilot study, an extract of date palm kernel was shown to reduce wrinkles by optical profilometry and visual assessment compared with placebo.

Tertiary therapies

Tertiary therapies have been popularized because they not only target the clinical characteristics of photoaged skin, but can also be used in intrinsic aging as well as cosmetic augmentation. There are very few well-designed published studies that have specifically examined the effect of these therapies on photoaging and its clinical phenotype. For that reason, these therapies are briefly reviewed with an emphasis on their role in photoaging.

Chemical peels. A variety of chemical peels, including $\alpha$-hydroxy acids (AHAs), salicylic acid, trichloroacetic acid, and phenol, are used to treat acne, acne scars, photodamage, and mottled hyperpigmentation. They are classified as superficial, medium, and deep, which correlate with the depth of injury induced. Portions of the epidermis and dermis are damaged with subsequent regeneration, resulting in a controlled wound and re-epithelialization with rejuvenation of skin.

Glycolic acid (GA) is an AHA superficial peel that improves skin texture and reduces fine wrinkling and the number of actinic keratoses. It can also thin the stratum corneum and epidermis, as well as increase dermal collagen thickness. GA is found in many skin creams and has been shown to modestly improve photodamage when used in this fashion. GA can also increase sunburn cell formation and sensitivity to UV-induced erythema. Therefore it may paradoxically enhance short-term sensitivity to the damaging effects of UV light.

Resurfacing techniques. Microdermabrasion exfoliates and ablates the superficial epidermis. Microcoblation uses low-frequency radiofrequency energy delivered via a recessed electrode bathed in saline solution on the skin. Both are hypothesized to increase dermal collagen thickness and type I procollagen mRNA with treatment. Significant increases in the thickness of papillary dermis and improved organization in elastin and collagen have been observed as well as improvements in hyperchromatic pigmentation. Microcoblation acutely gives rise to a zone of vasculopathy in the mid-epidermal layers. Both processes give similar results for texture, appearance, clarity, and oiliness when evaluated subjectively.

Laser systems. There are numerous applications for cutaneous laser surgery, including destruction of vascular and pigmented lesions, striae, verrucae, as well as dermal remodeling for treatment of photodamage. Some lasers work through selective photothermolysis where controlled destruction of a chromophore occurs without damage to surrounding normal tissue. Ablative and nonablative laser systems have been successfully used in the treatment of photodamage and wrinkles. Both methods increase collagen production; however, the exact mechanism by which this occurs is unknown.

Ablative laser systems. Ablative systems include the carbon dioxide (CO$_2$) and erbium:yttrium-aluminum-garnet (YAG) lasers. The CO$_2$ laser is considered the “gold standard.” Facial resurfacing with the CO$_2$ laser typically produces at least a 50% improvement in overall skin tone, wrinkle severity, and atrophic scar depth. The erbium:YAG laser, developed to reduce the morbidity associated with CO$_2$ laser resurfacing, has demonstrated comparable results with fewer side effects in some studies. The biochemical changes seen after CO$_2$ laser resurfacing include increased mRNA of several cytokines (IL-1$\beta$, TNF-$\alpha$, and TGF-$\beta$1), type I and type III procollagen, and MMPs. Undesired effects of ablative systems include hypertrophic scar formation and pigmented alterations. In addition, they induce significant morbidity until re-epithelialization occurs, which requires at least 1 week, and the full recovery period can be a month or more.

Nonablative laser systems. Nonablative systems are thought to induce collagen remodeling by creation of a dermal wound without disruption of the epidermis. They are popular among patients who are unwilling or unable to undergo the postoperative recovery associated with ablative procedures. They are much less effective than ablative systems in the treatment of photoaging but can reduce hyperpigmentation and telangiectases. The clinical efficacy of nonablative systems continues to be debated. For example, a controlled half-face study of the 1450-nm diode laser demonstrated significant clinical improvement in periorbital rhytides as well as increases in dermal collagen assessed histologically. However, in a separate study, 25 dermatologists clinically evaluated patients after 1450-nm diode treatment. Although all patients reported mild to moderate improvement, only 2 of the 25 dermatologists recorded a significant
positive treatment effect, suggesting that modest changes induced by the laser may not be clinically meaningful.

Radiofrequency technology

Radiofrequency devices produce an electric current that generates heat through resistance in the dermis and subcutaneous tissue. They have been shown to improve cheek and neck laxity in a pilot study. These clinical changes are thought to reflect collagen contraction followed by secondary collagen synthesis and remodeling. Adverse events such as erythema, soreness, and second-degree burning have been reported.

Botulinum toxins

Botulinum toxin A is a naturally occurring exotoxin produced by Clostridium botulinum that prevents local neuromuscular transmission. It was approved for cosmetic use by the Food and Drug Administration for glabellar lines in 2002. The toxin facilitates cleavage of synaptosomal associated membrane protein (SNAP)-25, which is required for exocytosis of acetylcholine, thereby inhibiting muscle contraction. Although botulinum toxin A does not directly reverse changes in the extracellular matrix caused by photodamage, it gives the appearance of rejuvenation by relaxation of the underlying musculature. In a large placebo-controlled trial, it significantly reduced glabellar line severity. The effects typically last 3 months.

Botulinum toxin B targets the synaptobrevin protein, ultimately inhibiting acetylcholine release. In a pilot study it was shown to be effective in the correction of crow's feet and was well tolerated. However, its use in the treatment of facial wrinkles has not yet been approved by the Food and Drug Administration.

Soft tissue augmentation

Soft tissue augmentation, or “fillers,” are designed to address the subcutaneous atrophy that accompanies senescence. Fillers have been used to treat fine lines and sallowness in photoaging, but have a greater market in intrinsically aged skin and for other cosmetic purposes. Some approaches are mentioned briefly herein.

In autologous lipomuflage, fat is typically harvested from one region and can then be frozen and used in staged injections. The results are thought to last longer than other methods, although no objective studies have been completed.

Bovine collagen has been regarded as the “gold standard” of injectable fillers. There are two commercially available products: an original bovine collagen preparation and a glutaraldehyde cross-linked bovine collagen that is more stable and longer lasting. Maintenance injections are required approximately every 4 to 6 months. Although these are effective fillers, drawbacks include immunogenicity and potential hypersensitivity reactions.

An acellular dermal graft derived from human cadavers contains collagen, elastin, and glycosaminoglycans. It is available in sheets, requiring an incision for placement, as well as in a micronized injectable form. Its advantage is that it is human in origin. When compared with bovine collagen, this human cadaver–derived dermal graft retains a higher percentage of the original implant volume. The usage of these products has decreased with the introduction of new fillers.

The hyaluronic acid (HA) derivatives, derived from rooster combs or through bacterial fermentation, are less immunogenic compared with bovine collagen preparations because HA is chemically identical across species. When tested in an animal system, a reduced inflammatory response and no signs of incompatibility were noted in the HA group compared with bovine collagen. In a 6-month randomized study the HA product was judged superior to bovine collagen by a wrinkle-severity rating score and global aesthetic improvement scale, with longer lasting effects.

A mixture of microspheres of polymethylmethacrylate (20%) and bovine collagen (80%) has been developed and is available outside the United States. One of its strengths is that the microspheres are too large to be phagocytosed, and therefore it is considered to last longer than other methods of augmentation.

EMERGING THERAPIES

Numerous compounds have demonstrated efficacy in experimental systems and may prove to have a clinical benefit for the treatment of photoaging (Table III).

Antioxidants

Oral soy isoflavones. Soy isoflavones can enhance the activity of endogenous antioxidant enzymes and protect against UV-induced aging. Mice fed a solution containing isoflavones (primarily genistein and daidzein) and chronically exposed to UV for 4 weeks exhibited significant decreases in skin roughness measured by optical profilometry. In addition, epidermal thickness was significantly lower and the level of procollagen higher in the isoflavone-treated group. Dose-dependent decreases in MMP induction by UV radiation were also noted in an in vitro study of human fibroblasts treated with isoflavones.
Topical genistein and N-acetyl cysteines. Topical genistein was shown to prevent c-Jun and collagenase up-regulation after UV exposure in human skin in vivo. Beyond its antioxidant activity, genistein is an inhibitor of tyrosine kinase activity and may inhibit signal transduction induced by UV light. Similar effects were found with the antioxidant N-acetyl cysteine, a precursor to glutathione.

Gluconolactone. Gluconolactone is a polyhydroxy acid, related to AHAs such as glycolic acid. Gluconolactone has antioxidant properties while sharing in some of the effects of AHAs. Pretreatment with gluconolactone was shown to reduce UV induction of elastin by 50% in murine fibroblast cultures, potentially through its free-radical scavenger activity. Gluconolactone has already been incorporated into numerous cosmetic preparations, apparently serving as a preventive treatment for solar elastosis.

Green tea polyphenols. Green tea polyphenols (GTPs) are potent antioxidants found in numerous skin care products. Oral administration of GTPs markedly inhibited UV-induced expression of MMP in mouse skin, which suggests that GTP has a potential anti-photoaging effect. Even in the absence of UV light, (-)-epigallocatechin-3-gallate, a component of green tea, was shown to inhibit the expression of various MMPs.

N-Furfuryladenine. N-Furfuryladenine (kinetin) is a synthetic plant growth hormone with antioxidant properties. It has been shown to decrease or delay some of the age-related changes that occur in human fibroblasts during serial passage in cell culture. It can also reduce ROS-mediated damage to DNA. Currently, there are no published clinical studies of this compound available for review; however, it has been introduced into cosmeceuticals and may be useful in patients who are unable to tolerate retinoids.

Other antioxidants. Dietary supplementation with lutein, a carotenoid, was shown to decrease UV-mediated inflammation and immunosuppression in a murine system. An antioxidant extract from pine trees was shown to protect mice from inflammation, immunosuppression, and carcinogenesis induced by UV light when applied immediately after UV exposure.

Iron chelators

Because MMP activation is dependent on iron, the iron chelator kojic acid was investigated to determine its potential preventive effects on photoaging. Kojic acid is produced by the fungus Aspergillus oryzae and is found in Japanese soy-based products. It has antioxidant properties and is a tyrosinase inhibitor that has been used in the treatment of hyperpigmentation disorders, such as melasma.

Pretreatment of mice with kojic acid before long-term UV exposure was found to reduce clinical assessments of wrinkling. Furthermore, UV-induced increases in dermal dermatan sulfate, chondroitin, epidermal hyperplasia, and dermal fibrosis were all reduced in the kojic acid–treated group when evaluated histologically. Kojic acid is currently incorporated into many Japanese cosmetic products.

Anti-inflammatory agents

The protective effects of topical hydrocortisone, naproxen, and ibuprofen were examined in the hairless mouse. All 3 compounds significantly prevented wrinkling and increases in collagen damage, elastosis, and dermal cellularity in hairless mice exposed to UV over a long period. Recently, celecoxib has been shown to reduce inflammation caused by short- and long-term UV exposure. Hairless mice treated with topical celecoxib have significant decreases in p53 activation and DNA damage 24-hours after UV exposure. When exposed to radiation over a long period, skin from celecoxib-treated mice demonstrated significant decreases in inflammatory markers, such as numbers of neutrophils, myeloperoxidase levels, and prostaglandin E2.

Novel compounds

Lipospondin. “Lipospondin” is a tripeptide linked to elaidic acid. It was designed to simultaneously activate latent TGF-β (through its peptide domain) and inhibit MMPs (through its lipophilic moiety, elaidic acid). It was able to up-regulate collagen and TIMP production and down-regulate MMP in fibroblast cultures; therefore “lipospondin” may show potential as a therapy for photoaging.
Oligodeoxynucleotide technology. Oligodeoxynucleotide technology uses synthetic decoy cis elements to block the binding of transcription factors to promoter regions of target genes. An NF-κB oligodeoxynucleotide has been developed and was shown to reduce UV-induced inflammatory changes (eg, swelling, leukocyte infiltration, epidermal hyperplasia, and accumulation of proinflammatory cytokines) when topically applied to mice. This experiment focused on the role of NF-κB in sunburn. As NF-κB also has a role in MMP induction and photoaging, modification of this pathway may prove to have a future preventive role in photoaging.

SUMMARY

Like all organs, skin undergoes characteristic changes with age. In addition, photoaging due to UV radiation causes undesirable changes in skin appearance. Recent advances in skin biology have elucidated mechanisms by which photoaging occurs and have given rise to new treatments to prevent and reverse this process. There is currently a wide array of options available for those persons seeking to improve the appearance of their skin, with even more exciting treatments, including novel antioxidants, new compounds, and receptor-selective retinoids, on the horizon.

Many thanks to Dr Lauren Hammock for supplying the photomicrograph.

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